NAMD – The Engine for Large-Scale Classical MD Simulations of Biomolecular Systems Based on a Polarizable Force Field

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ALCF Early Science Program Kick-*1*-Off Workshop Agenda
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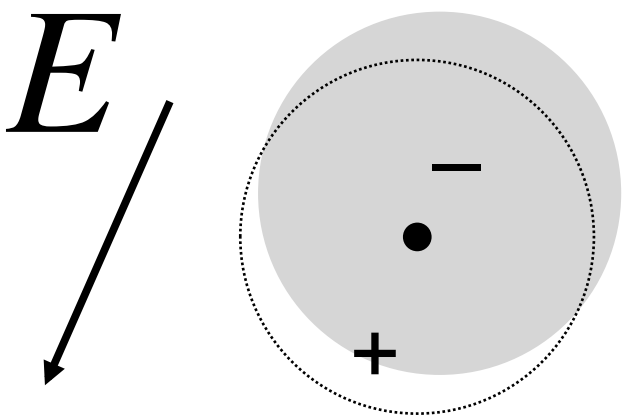
Basics of Induced Electronic Polarization



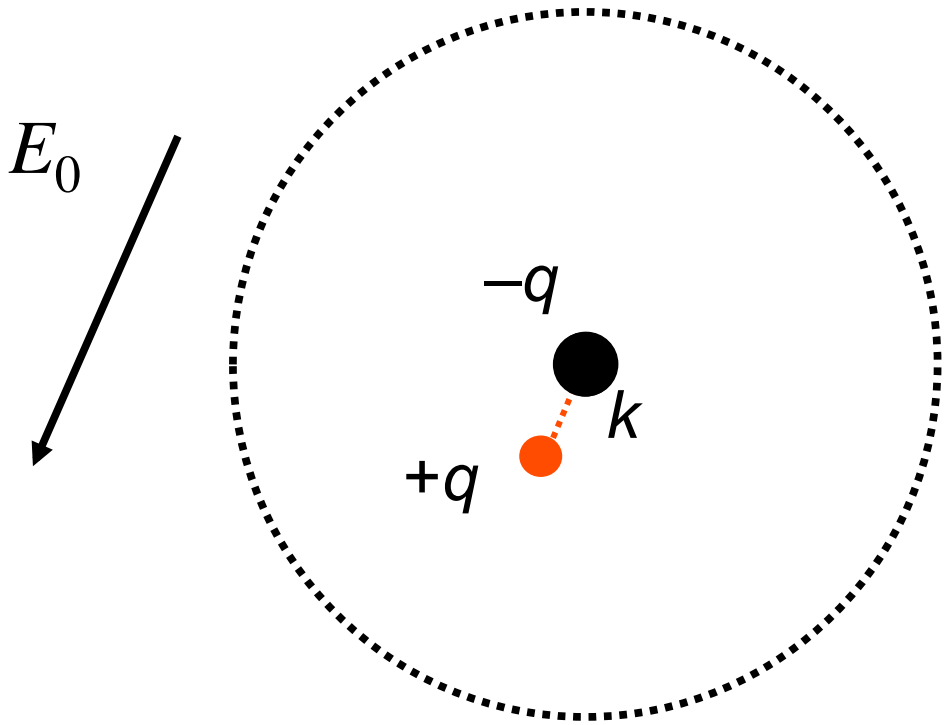
Influence of an external electric field

$$\langle \mu \rangle \approx 2 \sum_{n \neq 0} \frac{\langle \varphi_0 | \mu | \varphi_n \rangle \langle \varphi_n | \mu \cdot E | \varphi_0 \rangle}{(\varepsilon_n - \varepsilon_0)}$$

$$\langle \mu \rangle \approx 2 \frac{\langle \varphi_0 | \mu : \mu | \varphi_0 \rangle}{\Delta \varepsilon} \cdot E$$

$$\langle \mu \rangle \approx \alpha \cdot E$$

Classical Drude Oscillator Model



$$k\mathrm{d} = qE_{\mathrm{tot}}$$

$$\mu = d\,q$$

$$\mu = \alpha\,E_{\mathrm{tot}}$$

$$\alpha = \frac{q^2}{k}$$

$$U_{NB} = U_{LJ} + \sum_{i,j\neq i} \frac{q_i q_j}{r_{ij}} + \sum_i \frac{1}{2} K_D d_i^2$$

SCF with “Cold” Drude Oscillators

$$k_{\mathrm{D}}\mathbf{d}_i - q_{\mathrm{D},i}\mathbf{E}_i = \mathbf{0}$$

The oscillators are set at their local energy minimum at every timestep during a MD trajectory

$$\boldsymbol{\mu}_i^{\mathrm{SCF}} = \alpha_i \left[-\sum_{j\neq i} q_j \boldsymbol{\nabla}_i \left(\frac{1}{r_{ij}}\right) + \sum_{j\neq i} \boldsymbol{\mu}_j^{\mathrm{SCF}} \cdot \boldsymbol{\nabla}_i \boldsymbol{\nabla}_i \left(\frac{1}{r_{ij}}\right) \right]$$

$$U^{\mathrm{SCF}}(\{\mathbf{r}\}) \equiv U(\{\mathbf{r}\}, \{\mathbf{d}^{\mathrm{SCF}}\})$$

$$m_i \ddot{\mathbf{r}}_i = -\frac{\partial U^{\mathrm{SCF}}}{\partial \mathbf{r}_i}.$$

SCF dynamics is equivalent to keeping the oscillators at a temperature T* =0 K, “Cold” Drudes…

Dynamical “Hot” Drude Oscillators

$$(m_i - m_{\mathrm{D}})\ddot{\mathbf{r}}_i = -\frac{\partial U}{\partial \mathbf{r}_i}$$

$$m_{\mathrm{D}}\ddot{\mathbf{r}}_{\mathrm{D},i} = -\frac{\partial U}{\partial \mathbf{r}_{\mathrm{D},i}}$$

Drude oscillators are allowed to move dynamically as classical particles during a MD trajectory (“Hot” Drudes)

$$e^{-\beta U^{\mathrm{eff}}(\{\mathbf{r}\})} = \frac{\int d\{\mathbf{d}\}\, e^{-\beta U(\{\mathbf{r}\},\{\mathbf{d}\})}}{\int d\{\mathbf{d}\}\, e^{-\beta U_{\mathrm{self}}(\{\mathbf{d}\})}}$$

$$U(\{\mathbf{r}\},\{\mathbf{d}\}) = U^{\mathrm{SCF}}(\{\mathbf{r}\}) + \sum_i \delta\mathbf{d}_i \cdot \left.\frac{\partial U}{\partial \mathbf{d}_i}\right|_{\mathrm{SCF}} + \frac{1}{2}\sum_{ij} \delta\mathbf{d}_i \cdot \left.\frac{\partial^2 U}{\partial \mathbf{d}_i \partial \mathbf{d}_j}\right|_{\mathrm{SCF}} \cdot \delta\mathbf{d}_j + \ldots$$

$$e^{-\beta U^{\mathrm{eff}}(\{\mathbf{r}\})} = e^{-\beta U^{\mathrm{SCF}}(\{\mathbf{r}\})} \times \frac{\int d\{\delta\mathbf{d}\}\, e^{-\frac{1}{2}\beta \sum_{ij} \delta\mathbf{d}_i \cdot \frac{\partial^2 U}{\partial \mathbf{d}_i \partial \mathbf{d}_j} \cdot \delta\mathbf{d}_j}}{\int d\{\delta\mathbf{d}\}\, e^{-\beta U_{\mathrm{self}}(\{\delta\mathbf{d}\})}}$$

$$U^{\mathrm{eff}}(\{\mathbf{r}\}) = U^{\mathrm{SCF}}(\{\mathbf{r}\}) - \frac{3}{2} k_{\mathrm{B}} T \sum_{ij} \frac{\alpha_i \alpha_j}{r_{ij}^6} + \ldots$$

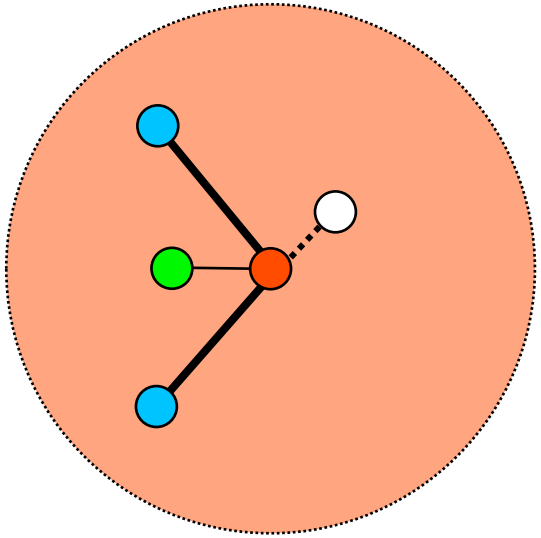
“Hot” Drude dynamics is closely related to SCF system

Lamoureux & Roux (JCP, 2004)

Polarizable Water

SWM4-DP:

Simple Water Model with 4 sites and Drude Polarizability



Lamoureux, MacKerell & Roux (JCP, 2004)
Lamoureux et al (CPL, 2005)

Properties of the SWM4-NDP model compared to those of the original SWM4-DP model and the non-polarizable TIP3P model

	Expt.[a]	TIP3P[b]	SWM4-DP[c]	SWM4-NDP[d]
Monomer				
μ_0 (D)	1.85	2.347	1.85	1.85
α (Å^3)	1.44		1.04252	0.97825
Q_{xx} (D Å)	−0.134	−0.080	−0.2421	−0.2479
Q_{yy} (D Å)	2.626	1.762	2.4068	2.4247
Q_{zz} (D Å)	−2.493	−1.681	−2.1647	−2.1768
Dimer (0 K)				
U_{dimer} (kcal/mol)	−5.4	−6.50	−5.18	−5.15
d_{OO} (Å)	2.98	2.74	2.82	2.83
θ_A (°)	58	20	70	71
μ_{dimer} (D)	2.643	3.866	2.087	2.062
Bulk liquid (298.15 K)				
Δu (kcal/mol)	−9.92	−9.82	−9.927	−9.923
$\langle v \rangle$ (Å^3)	29.94	29.9	29.93	29.91
$\langle \mu \rangle$ (D)		2.347	2.456	2.461
D (10^{-5} cm^2/s)	2.3	5.1	2.30 ± 0.04	2.33 ± 0.02
ϵ	78.4	92 ± 5	79 ± 5	79 ± 3
η (cp)	0.89			0.70 ± 0.05
τ_D (ps)	8.27, 8.32, 8.40		11.1 ± 1.5[e]	11 ± 2
τ_{NMR} (ps)	2.1			1.87 ± 0.03
ΔG_{hyd} (kcal/mol)	−6.32, −4.4, −5.74, −6.33	−6.10	-6.0 ± 0.1[f]	-5.9 ± 0.1[g], −6.0[h]
Air/water interface (298.15 K)				
γ (dyn/cm)	72.0	52.7	66.9 ± 0.9	67 ± 4
$\Delta\phi$ (mV)		−500	−540	−545

[a] Shear viscosity η from [14], τ_D from [15–17], τ_{NMR} from [18], ΔG_{hyd} values from [19–22] ([20] at 27 °C). For other properties, see [2] and references therein.

[b] Ref. [6] for the model, γ and $\Delta\phi$ from [23], ΔG_{hyd} from [24].

[c] Ref. [2], except for ΔG_{hyd}.

[d] This work.

[e] Correct value, obtained from trajectories of [2].

[f] From TI calculation in bulk water, using 100 ps per window instead of 300.

[g] From TI calculation in bulk water.

[h] From PMF calculation in the slab system.

Lamoureux et al, CPL 2005

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JCTC Journal of Chemical Theory and Computation

Simulating Monovalent and Divalent Ions in Aqueous Solution Using a Drude Polarizable Force Field

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Table 2. Properties of Alkali Cations, Halide Anions, and Divalent Cations with Drude Polarizable Models

ion	U_{min} [a]	d_{min} [b]	ΔH [c]	r_{max}	g_{max}	r_{min}	g_{min}	N_c	D [d]	ΔG_{hydr}^{real} [e]	$\Delta\Delta G_{hydr}$ [f]
Li^+	−35.9 (−35.2)	1.91 (1.87)	−35.6 (−34.0, −34.0)	2.02	12.50	2.56	0.00	4.0	1.30 (1.03)	−120.5	−24.2 (−23.8 to −26.2)
Na^+	−24.6 (−24.3)	2.25 (2.26)	−24.4 (−24.0, −25.0)	2.38	7.42	3.24	0.20	5.6	1.58 (1.33)	−96.3	−17.3 (−16.7 to −17.7)
K^+	−17.9 (−17.8)	2.62 (2.64)	−17.6 (−17.9, −18.1)	2.74	4.80	3.56	0.45	6.9	2.20 (1.98)	−78.6	−5.2 (−4.9 to −5.4)
Rb^+	−15.7 (−16.1)	2.79 (2.79)	−15.2 (−15.9, −16.0)	2.90	4.04	3.80	0.62	8.1	2.44 (2.07)	−73.7	−7.1 (−5.5 to −7.7)
Cs^+	−13.3 (−14.1)	3.05 (2.99)	−12.5 (−13.7, —)	3.16	3.25	4.10	0.75	9.7	2.56 (2.06)	−66.5	
F^-	−23.5 (−25.9)	2.53 (2.44)	−23.2 (−23.3, −23.3)	2.72	4.77	3.34	0.37	5.5	1.33 (1.48)	−108.0	−30.0 (−13.4 to −30.6)
Cl^-	−14.0 (−14.4)	3.09 (3.11)	−13.7 (−13.1, −14.4)	3.16	3.15	3.78	0.72	6.5	1.82 (2.03)	−78.4	−6.5 (−3.3 to −6.9)
Br^-	−12.4 (−12.7)	3.26 (3.26)	−11.9 (−12.6, −13.0)	3.28	2.70	3.96	0.75	6.8	1.85 (2.08)	−71.6	−8.5 (−7.7 to −11.1)
I^-	−10.2 (−10.6)	3.56 (3.50)	−9.7 (−10.2, −10.5)	3.50	2.28	4.16	0.90	7.1	2.02 (2.05)	−63.1	
Zn^{2+}	−100.0 (−96.3)	1.82 (1.86)	−99.4 (−103.1)	2.14	17.2	3.08	0.0	6.0	0.61 (0.70)	−460.2	−90.3 (−107.6)
Mg^{2+}	−89.4 (−77.9)	1.86 (1.93)	−89.0 (−81.8)	2.06	19.0	2.72	0.0	6.0	0.82 (0.71)	−447.2	−77.3 (−77.7 to −80.3)
Ca^{2+}	−55.6 (−54.9)	2.18 (2.25)	−55.1 (−56.5)	2.28	16.9	2.76	0.0	6.0	0.96 (0.79)	−369.9	−32.7 (−29.8 to −32.9)
Sr^{2+}	−45.2 (−40.6)	2.30 (2.52)	−44.7 (−)	2.42	11.9	3.20	0.0	7.2	0.96 (0.79)	−337.2	−27.2 (−27.9 to −31.1)
Ba^{2+}	−37.7 (−34.0)	2.56 (2.73)	−37.3 (−)	2.68	10.4	3.30	0.1	8.2	0.97 (0.85)	−310.0	

JCTC Journal of Chemical Theory and Computation

Determination of Electrostatic Parameters for a Polarizable Force Field Based on the Classical Drude Oscillator

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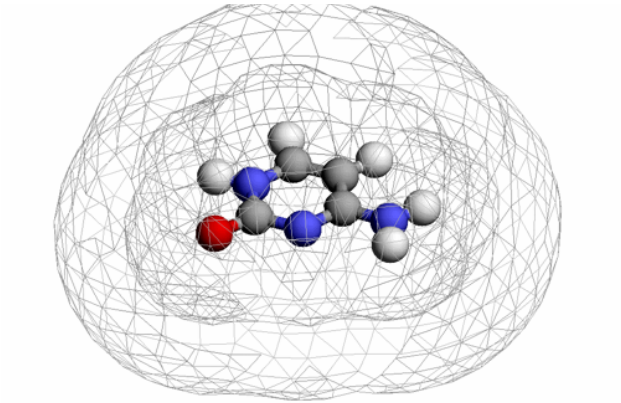
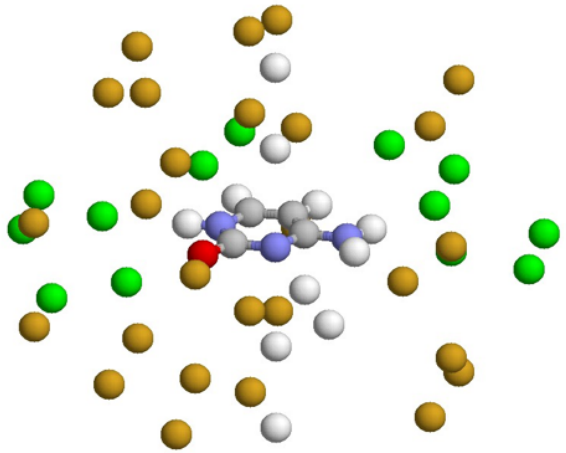


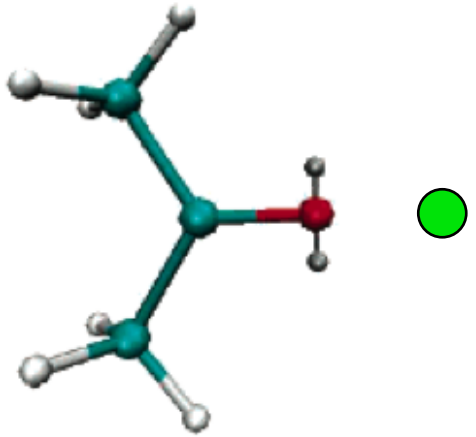


$$\chi^2_{\phi}[q_{\mathrm{c}},q_{\mathrm{D}}] = \sum_{p,g}\left(\phi^{QM}_{pg} - \phi^{MM}_{pg}\right)^2$$

Is induced polarization a reasonable model of QM?

$$E = \int_0^{q_{\text{test}}} dq\, \phi(q)$$

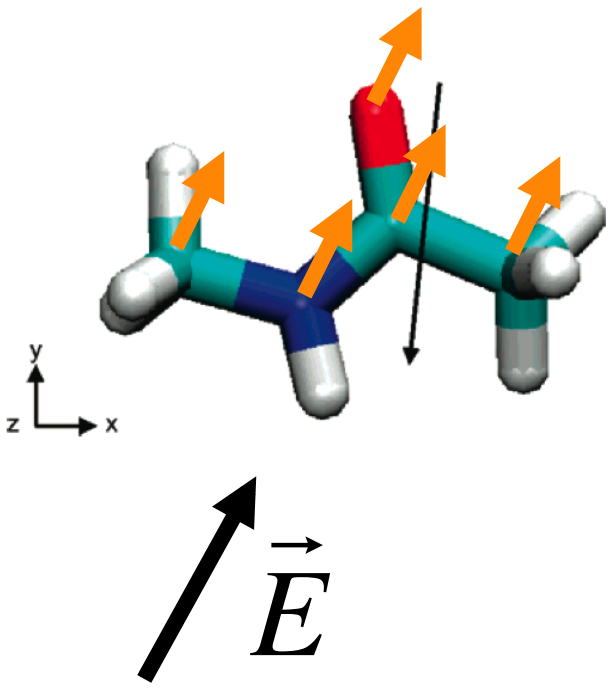
$$E^{\text{lr}} = Aq_{\text{test}} + \frac{1}{2}Bq_{\text{test}}{}^2$$



Charge	$q\phi_{\text{stat}}$	$0.5q\phi_{\text{pol}}$	E^{lr}	E	E_{diff}
0.5	−13.1	−3.4	−16.5	−16.3	0.2
1.0	−26.2	−15.3	−41.5	−40.2	1.3
2.0	−52.4	−115.0	−167.4	−128.8	38.6

Harder, Anisimov, Vorobyov, Lopes, Noskov, MacKerell & Roux (JCTC, 2006)

N-methyl acetamide



The Molecular Dipole of NMA[a]

dipole	QM	Drude (unscaled/vthole)
μ_x	0.36	0.35
μ_y	3.89	3.84
μ_z	0.06	0.0
μ	3.9	3.9

Molecular Polarizabilities of NMA[a]

$\bar{\alpha}$	QM	Drude (unscaled/vthole)
α_{xx}	9.4	9.2
α_{xy}	0.4	0.6
α_{xz}	0.0	0.0
α_{yy}	8.0	8.0
α_{yz}	0.0	0.0
α_{zz}	6.0	6.4
$TR(\bar{\alpha})$	7.8	7.9

The Temperature Dependence of the Dielectric Constant from Simulations at 308 and 373 K[a]

NMA	ϵ ($T = 308$ K)	ϵ ($T = 373$ K)
experiment	170	100
Drude	150 ± 15	92 ± 5
CHARMM	55 ± 5	37 ± 2

Harder et al (J Phys Chem B 2008)

Dual Langevin Thermostats for high performance scalable NAMD

$$m_i \ddot{\mathbf{R}}_i = \mathbf{F}_{\mathbf{R},i} - \gamma \dot{\mathbf{R}}_i + \mathbf{f}_i$$

$$m'_i \ddot{\mathbf{d}}_i = \mathbf{F}_{\mathbf{d},i} - \gamma' \dot{\mathbf{d}}_i + \mathbf{f}'_i$$

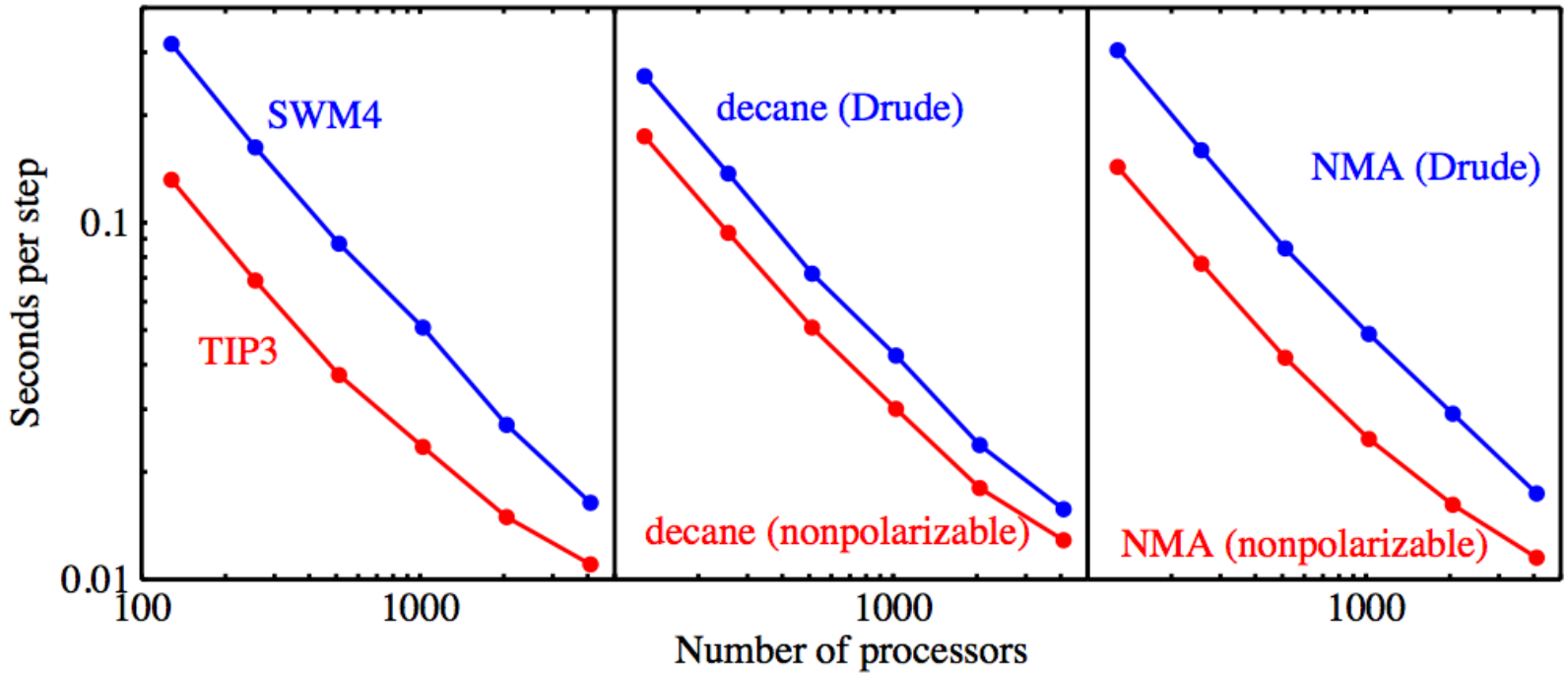
$$\mathbf{F}_{\mathbf{R},i} = -\frac{\partial U}{\partial \mathbf{r}_i} - \frac{\partial U}{\partial \mathbf{r}_{\mathrm{D},i}},$$

$$\mathbf{F}_{\mathbf{d},i} = -\left(1 - \frac{m_{\mathrm{D}}}{m_i}\right)\frac{\partial U}{\partial \mathbf{r}_{\mathrm{D},i}} + \left(\frac{m_{\mathrm{D}}}{m_i}\right)\frac{\partial U}{\partial \mathbf{r}_i}.$$

$$\mathbf{f}_i = \sqrt{2\gamma k_B T / m_i}\, R(t)$$

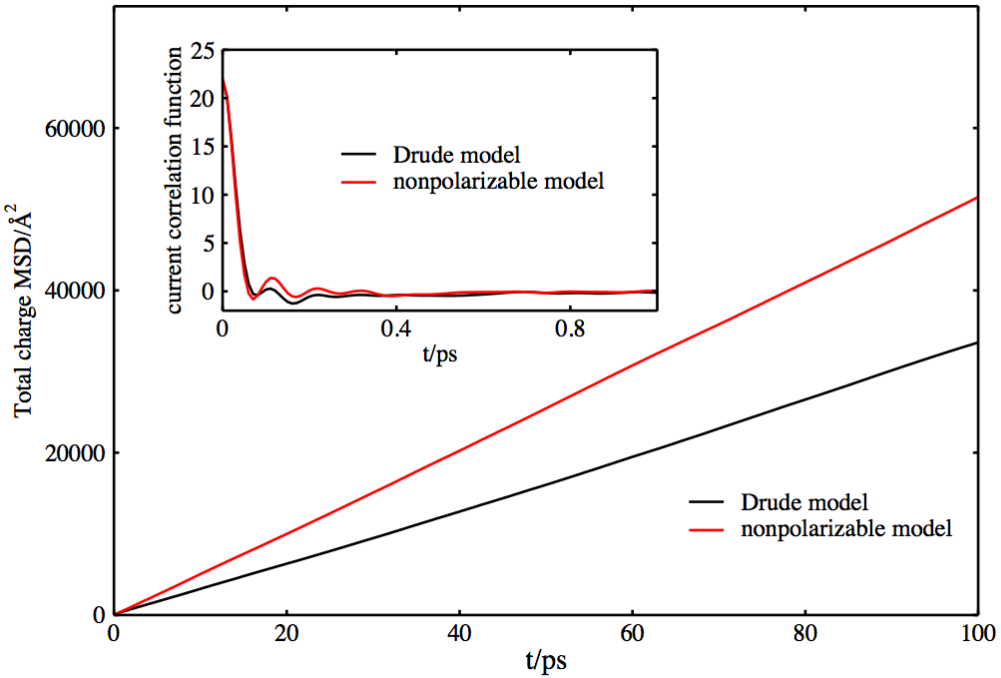
$$\mathbf{f}_i^{\star} = \sqrt{2\gamma' k_B T^{\star} / m'_i}\, R^{\star}(t)$$

Drude model implemented in NAMD: Tests on Blue Gene/P



A) Cubic box of 72000 water molecules (ratio 1:2)
B) Cubic box of 8576 decane molecules (ratio 1:1.6)
C) Cubic box of 18944 NMA molecules (ratio 1:1.8)

Conductivity of Aqueous Physiological Salt Concentration



Conductivity [mS/cm]

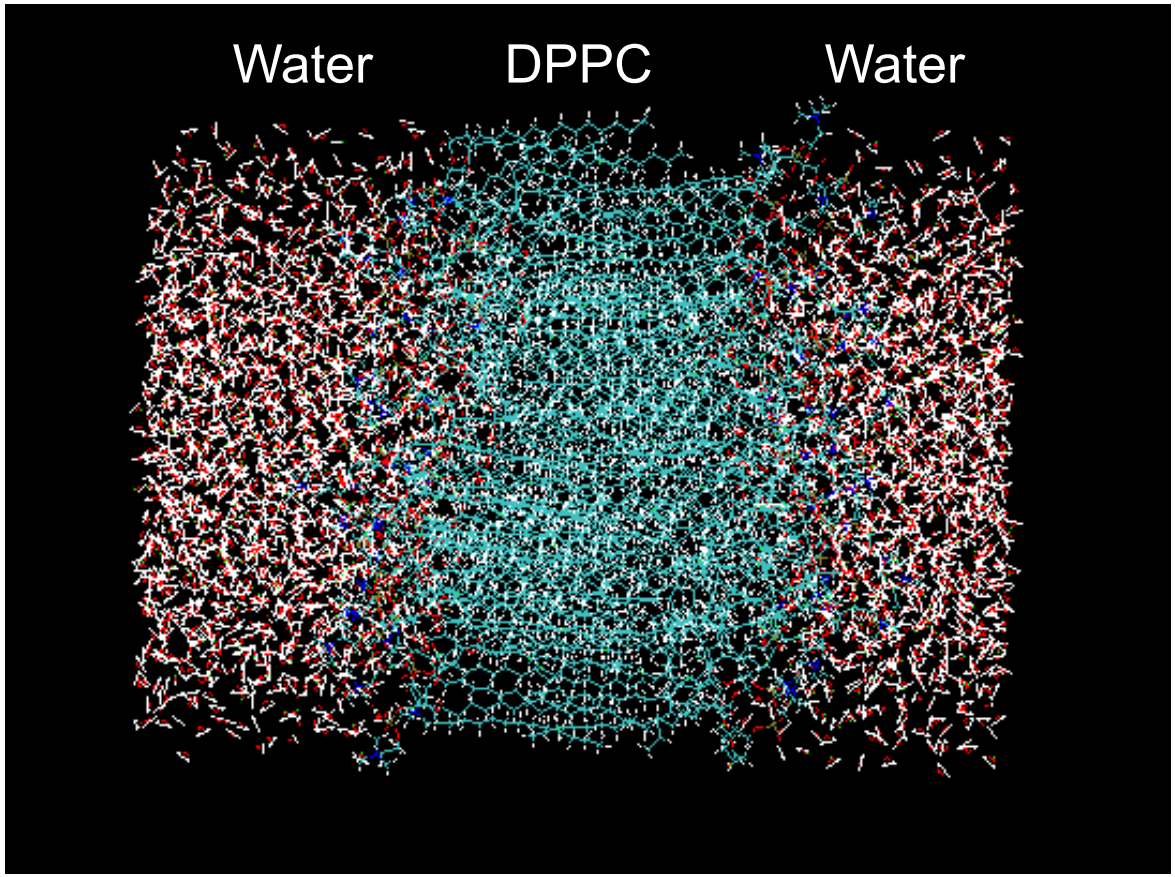
Drude	17.3 (14.7)
Additive	28.2 (24.4)
Experimental	16

$$\sigma = \lim_{t\to\infty} \frac{e^2}{6tVk_BT} \sum_{ij}^{N} z_i z_j \left\langle [\mathbf{R}_i(t) - \mathbf{R}_i(0)] \cdot [\mathbf{R}_j(t) - \mathbf{R}_j(0)] \right\rangle$$

$$\sigma = \frac{e^2}{3Vk_BT} \int_0^\infty dt \left\langle \left[\sum_i \mathbf{v}_{i+}(t) - \sum_j \mathbf{v}_{j-}(t) \right] \left[\sum_i \mathbf{v}_{i+}(0) - \sum_j \mathbf{v}_{j-}(0) \right] \right\rangle$$

Wei jiang

DPPC bilayer representative configuration



(32+32) DPPC bilayer

Ed Harder, Janamejaya Chowdhary

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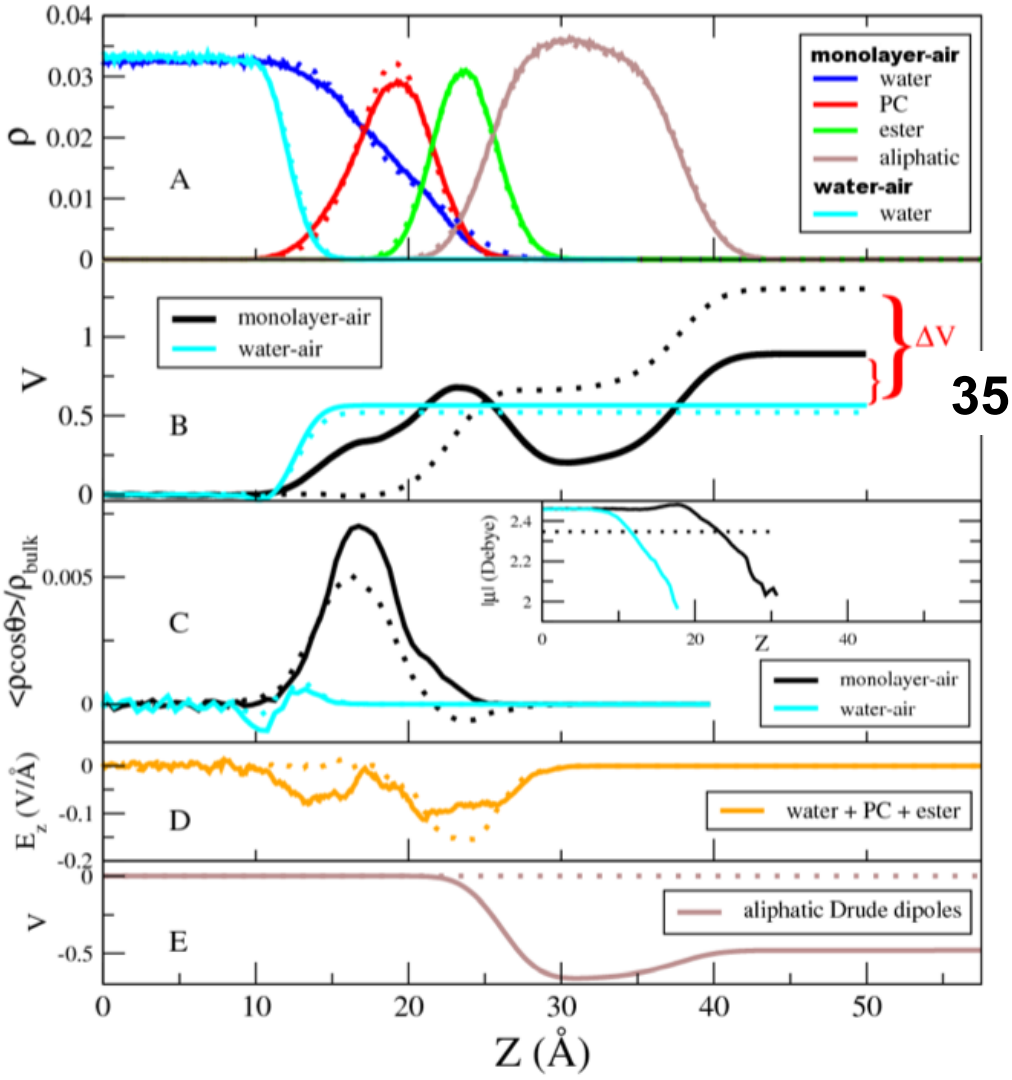
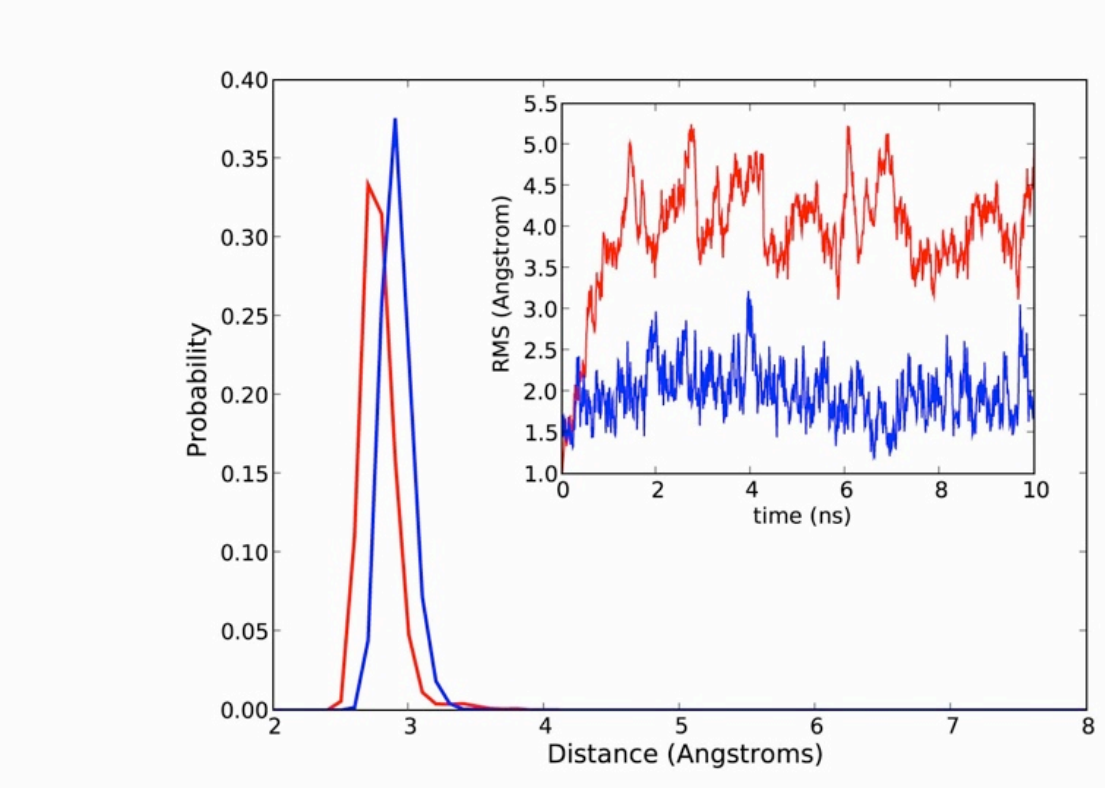
Many-Body Polarization Effects and the Membrane Dipole Potential

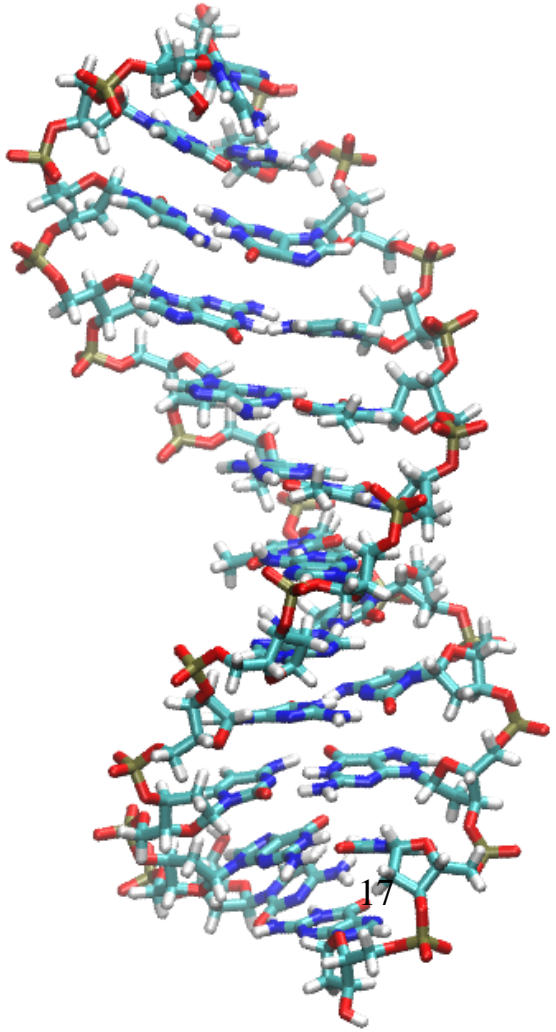
Edward Harder,† Alexander D. MacKerell, Jr.,*,‡ and Benoît Roux*,†



350 mV

Additive and Drude simulations of duplex DNA (EcoR1)





additive C27 and Drude

Polarizable Drude FF Status

- Small molecular optimization near completion
- Polarizability scaling to reproduce dielectric
- Lone pairs on H-bond acceptors
  - Interactions as a function of orientation
- Anisotropic atomic polarizability
  - Polarization response as a function of orientation
  - Interactions with ions
- Atom-based Thole Scale Factor
  - Molecular polarization tensor, dielectric constant
- LJ parameters on Drudes and lone pairs
  - Interaction with ions
- Electrostatic damping: flat well, higher order restraining potential
- Pairwise-specific LJ terms (NBFIX) with water
  - Systematic overestimation of free energy of solvation
- Phospholipid bilayer membranes, protein, nucleic acids
- Implementation in high performance scalable NAMD